Remarks

Information Disclosure Statement

For the references CA, CB, and CC, which are in Chinese. The inventors will consider the translation at least the abstracts of the same for submission with the PTO.

Specification

Applicants amended the Abstract as suggested by the Examiner. The term "said" has been removed.

Claim Rejections – 35 USC § 112

Regarding rejections under 35 USC § 112, the Examiner deems that the scopes of claims 1 and 2 are indefinite, respectively, because a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation is considered indefinite. Applicants amended the claims to overcome the rejections.

Applicants have amended claims 1 and 2 and added claims 3-4 and believe that such amended claims 1-4 are definite in their scope. The narrower range is now moved from claim 1 to claim 2. The subject matter in the new claims 3-4 can be found in previously filed claim 2 and specification. No new matter has been added.

Claim Rejections – 35 USC § 103

Regarding rejections under 35 USC § 103, the Examiner alleges that claims 1 and 2 are obvious over the cited references within the meanings of 35 USC § 103(a).

Applicants respectfully traverse these rejections for the following reasons.

Giao et al. discloses a combinational use of dihydroartemisinin, piperaquine, trimethoprim and primaquine, White discloses use of artemisinin and derivatives thereof in combinations and generally mentions their combinaiton with other antimalarial drugs, Klayman mainly discloses the structure, antimalarial activity and mechanism of action for artemisinin, Lai mentions artemisinin and derivatives thereof and EP 0290959 relates to a combination

comprising artemisinin, a derivatives thereof and primaquine. However, none of those documents discloses, teaches or suggests the present combination: artemisinin, piperaquine, and primaquine in a specific ratio. In order to arrive at the present invention, a person skilled in the art has to perform tremendous amount of work to screen the unlimited possible combinations and ratios in the prior art, which is not a "mere optimization" as suggested by the Examiner. Therefore, it is not obvious for a person skilled in the art to reach the present inventive combination.

Moreover, the present inventive combination and ratio are demonstrated to be advantageous over those in the prior art references.

1. Compared to the formulations in the prior art, the formulation with the claimed combination of the present application has surprisingly less side effects (see the attached Inventors' Declaration under Rule 1.132). Therefore, the formulation of the invention improves the compliance, especially facilitates the patients in the less developed regions to receive full term and sufficient treatment to enhance the effect of the treatment and prevention of malaria.

As indicated in the Inventors' Declaration, the present combination was used in clinic trials to treat the patients with malaria and compared with the formulation of dihydroartemisinin and piperaquine phosphate for the incidence of side effects expressed in percentage (%). The results indicate the inventive combination surprisingly decreased side effects such as reduced appetite, (from 2.8% to 1.4%), nausea (from 6.6% to 3.2%), vomiting (from 6.6% to 2.1%), diarrhea (from 2.8% to 1.0%), abdominal pain (from 1.9% to 1.0%), headache (from 2.8% to 0.8%), dizziness (from 4.7% to 1.4%), insomnia (from 2.8% to 0.6%), and tiredness (from 0.9% to 0.6%).

The data presented by the inventors show that the incidence of side effects caused by the present combination is lower than that caused by the formulation of dihydroartemisinin + piperaquine phosphate, and thus the present combination is surprisingly safer and less adverse to malaria patients than the formulation of dihydroartemisinin + piperaquine phosphate.

2. Compared to the formulations in the prior art, the formulation with the claimed combination of the application has a better stability and, thus, only two dosages are needed. This

advantage in combination with the surprisingly decreased side effects would help in malaria patients' receiving full term and sufficient treatment, especially in less developed countries.

3. Compared with the formulations in the prior art, the formulation with the claimed combination of the application has a low cost of manufacture. Artemisinin is obtained as a pure product directly by extracting the Chinese herb Artemisia apiacea, while derivatives of artemisinin are prepared by using artemisinin as the starting material, and the cost for producing derivatives of artemisinin is higher than that for artemisinin extracted from the Chinese herb. Malaria is a major cause of persistent poorness in the less developed countries in Africa and Southeastern Asia and thus reducing the costs of the drugs is very important for most of the patients in those countries to afford the drugs.

Based on the above reasons, the applicant believes that claims 1-4 are not obvious over the teaching, suggestion, and motivation in the prior art references cited by the Examiner.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 13796-00002-US from which the undersigned is authorized to draw.

Respectfully submitted,

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